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The Impact of Inter-fraction Set-up Errors on the Probability of Pulmonary and Cardiac Complication in Left-sided Breast Cancer Patients

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The Impact of Inter-fraction Set-up Errors on the Probability of Pulmonary and Cardiac Complication in Left-sided Breast Cancer Patients

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ABSTRACT

Purpose: This study evaluated the impact of patient set-up errors on the probability of pulmonary and cardiac complications in the irradiation of left-sided breast cancer.

Methods and Materials: Using the CMS XiO Version 4.6 (CMS Inc., St Louis, MO) radiotherapy planning system's NTCP algorithm and the Lyman –Kutcher-Burman (LKB) model, we calculated the DVH indices for the ipsilateral lung and heart and the resultant normal tissue complication probabilities (NTCP) for radiation-induced pneumonitis and excess cardiac mortality in 12 left-sided breast cancer patients.

Results: Isocenter shifts in the posterior direction had the greatest effect on the lung V20, heart V25, mean and maximum doses to the lung and the heart. Dose volume histograms (DVH) results show that the ipsilateral lung V20 tolerance was exceeded in 58% of the patients after 1cm posterior shifts. Similarly, the heart V25 tolerance was exceeded after 1cm antero-posterior and left-right isocentric shifts in 70% of the patients. The baseline NTCPs for radiation-induced pneumonitis ranged from 0.73% - 3.4% with a mean value of 1.7%. The maximum reported NTCP for radiation-induced pneumonitis was 5.8% (mean 2.6%) after 1cm posterior isocentric shift. The NTCP for excess cardiac mortality were 0 % in 100% of the patients (n=12) before and after set-up error simulations.

Conclusions: Set-up errors in left sided breast cancer patients have a statistically significant impact on the Lung NTCPs and DVH indices. However, with a central lung distance of 3cm or less (CLD <3cm), and a maximum heart distance of 1.5cm or less (MHD<1.5cm), the treatment plans could tolerate set-up errors of up to 1cm without any change in the NTCP to the heart.

Keywords: *NTCP, breast cancer radiotherapy, radiation pneumonitis, excess cardiac mortality.*

INTRODUCTION

Radiation therapy remains a vital modality in the management of breast cancer patients. A relatively good prognosis is shown in early detected breast cancer patients (1). The need for accuracy and precision in targeting the desired volumes is imperative as it not only improves success in the treatment but also the normal tissue will be spared. Many factors have been investigated that can affect the accuracy of the treatment delivery in breast cancer patients. Various researchers reported random or inter-fraction set-up errors of magnitude between 1.7mm -5.8mm and systematic errors between 1.0mm-14.4mm (2, 3).

There has been an increase in the reports of radiotherapy induced cardiovascular disease in the past 10 years (4). In breast cancer, this increase was stimulated by expert reports of radiation induced myocardial infarction, coronary revascularization, or death from ischemic heart disease. Darby, Ewertz and McGale, *et al* (4) suggests that the magnitude of the risk after any given dose to the heart is uncertain. A population-based case–control study of 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark revealed mean doses to the whole heart of 4.9 Gy (ranging 0.03 to 27.72). Several studies have suggested that exposures at this level can cause ischemic heart disease (5, 6, and 7). In addition to cardiac complications, radiation induced pneumonitis which is one of the most significant complications has been reported in breast cancer studies manifesting within the period of one to eight months after radiotherapy (10).

Recent studies have made an effort to estimate the pulmonary and cardiac complication risks involved in the radiation treatment of breast cancer. Long term follow-up data and two dimensional (2D)-radiographic parameters such as the central lung distance (CLD) and the maximum heart distances (MHD) were used to estimate the probability of complications after radiotherapy (8, 9 and 10). However, there are controversial reports on the correlation

between these radiographic parameters and the published complication probabilities (2, 6, and 7).

With the development of computerized tomography (CT) based planning methods there has been an improvement in dose coverage and the ability to calculate relevant dose distributions in organs at risk (OAR)(8). The dose volume histograms (DVHs) generated in CT-based plans can allow clinicians to use normal tissue complication probabilities (NTCP) models (9, 10) to estimate the risk of complications in normal organs. The heart and the lungs are among the organs that have been most successfully described by NTCP models that are widely available today. Many authors have used these NTCP models and parameterisations to determine the risk of complications that can arise from different breast cancer treatment techniques (6, 11 and 13). Quantec reviews have been helpful as they reported several aspects that must be considered when applying NTCP models and dose volume constraints to clinical planning (11). The aim of this study was to determine the impact of patient set-up errors on the probability of pulmonary and cardiac complications in irradiation of left-sided breast cancer.

MATERIALS AND METHODS

Patient selection and treatment planning

This investigation was carried out using CT data planned using a CMS XiO Version 4.6 (CMS Inc.,St Louis, MO) treatment planning system. Twelve left-sided female breast cancer patients treated between January 2011 and January 2012 were selected. All treatment plans had CT series that were composed of 2.5 mm slices based on the institution breast CT simulation protocol. A GE Light speed (GE Medical Systems) CT scanner was used. During CT scanning, the radiation oncologist determined the extent of the breast parenchyma, on the superior aspect, inferior and the lateral aspect. The planning volumes were determined by radio-opaque wires that were used to follow the radiation oncologist's markings on the patient skin.

The tangential breast plans (no supraclavicular field) were optimized by use of wedges and or field in field (FIF) segments. Appropriate beam weights were applied, 6MV and/or 18 MV photon energy was used depending on the breast separation. Multi-leaf collimators (MLC's) were used to shape the radiation fields in order to spare the lung and the heart. The maximum allowed central lung distance was 3cm. The maximum amount of the heart allowed in the radiation field was 1.5cm. The total prescribed treatment dose was 50Gy delivered in 25 fractions.

Delineation of organs at risk (OAR)

The whole heart and the ipsilateral lung were outlined in all patients. The contoured heart volume included the myocardium (heart muscle) and the interior chambers (the left and right atrium and the ventricles). The pulmonary trunk, ascending aorta and the superior vena cava were not included in the heart volume contoured. The entire OAR volumes were contoured

first by the medical dosimetrist and then evaluated by the radiation oncologist. All the plans selected for this study were contoured by the same dosimetrist and the same radiation oncologist.

Calculation of the Pulmonary and Cardiac NTCP

Using the Lyman –Kutcher-Burman (LKB) model, we were able to input the NTCP parameters to calculate the pulmonary and cardiac NTCPs. The schematic diagram for the NTCP calculations is shown in figure 1. The first objective was to generate dose volume data (DVH) for the heart and ipsilateral lung before introducing error shifts on the treatment plans. This is the first step in the NTCP calculation flow chart as outlined by Kwa *et al* (23). We had to determine the DVH parameters that would be compared to the ones calculated after simulating the set-up errors. The lung DVH parameters for both the heart and the lung were taken from the Quantec reviews (14, 16). In regards to heart, for each patient the partial volume of the heart receiving more than 25Gy, V25 (cm^3) and the mean heart dose were obtained. The DVH parameters for the lung recorded include the V20 (cm^3) and the mean lung dose.

After recording the baseline NTCPs on the original isocenter, the planning isocenter was shifted in the magnitude of 3mm, 5mm, and 10mm in three independent directions(x, y, and z) to simulate set- up errors in a method similarly used by Hector *et al* (18) and Prabhakar *et al* (19). The normal tissue complication probabilities (NTCP) for excess cardiac mortality after 10-15 years and pneumonitis was calculated using 2Gy per fraction and the Lyman model as described by Burman *et al* (9).

Selection of Normal tissue complication probability (NTCP) parameters

In the Quantec reviews, Semenenko and A Li (20) highlighted a difficulty in justifying the most accurate parameters for use due to a large number of parameter estimates available in literature. The lung NTCP parameters used in this study quoted were based on Semenenko and A Li (20) whose study included the lung density corrections. These published Lymen and Kutcher model parameters for radiation-induced pneumonitis were based on analysis of various multi-institutional toxicity data (15, 21). They reported parameters considering the lung both as a single and paired organ. In this study, the following ipsilateral lung parameters were used; m = 0.35, n=1 and TD50 = 37.6Gy. The NTCP parameters for calculating excess cardiac mortality using the LKB model were based on a study by Canney *et al* (22) as shown in table 1.

Statistical Analysis

Descriptive statistics (means, medians and range) were used to report the calculated NTCP and DVH indices. The difference between the population means for the lung V20 and heart V25 DVH indices and the lung NTCP predictions between data with no isocenter shifts and the data with various isocenter set-up errors was tested for statistical significance using a paired Student's *t*-test comparison. The significance level used was 5% for the two-tailed test performed using XLSTAT version 2012.2.02.

RESULTS

The ipsilateral lung (V20), heart (V25) and mean doses.

The DVH indices for the ipsilateral lung and the heart were calculated before and after the set-up error simulations.

a. DVH indices before the set-up error simulations

Table 2 shows the ipsilateral lung and heart DVH indices for each patient before set-up error simulation (n=12). These values were then used as a baseline for comparison after each set-up error simulations. The average V20 (n=12) was 16.38Gy (range 10.5-21.8Gy), whereas the average mean lung dose delivered to the ipsilateral lung was 8.66Gy (range 5.43-11.6 Gy). The average V25 value for the heart was 6.3% whereas the mean heart dose was 6.4Gy. In one patient, a higher baseline mean heart dose was recorded due to the anatomy of the patient, though the maximum lung heart distance was less than 1,5cm.

b. DVH indices after the set-up error simulations

The DVH indices were analysed again after the set-up error simulations of 0.3cm, 0.5cm and 1cm. Tables 4, 5 and 6 shows a comparison between the baseline DVH indices and those recorded after the isocentric shifts. As shown in table 6, the maximum relative change in the population mean for the Lung V20 was recorded in the AP shift (16.43Gy to 23.3Gy), $p<0.0001$. Similarly, for the heart, the greatest increase in V25 was in the AP direction after 1cm shifts (6.26Gy to 12.57Gy), $p=0.002$.

The calculated NTCP values for the Ipsilateral Lung and the Heart.

NTCP paramaters published by Canney et al (33) (excess cardiac mortality endpoint) and Semenenko and A Li (pnemonitis) were used in the calculations (Table 1). The NTCP for the ipsilateral lung and the heart were calculated before and after the set-up error simulations.

a. *NTCP calculations before set-up error simulations.*

In addition to the DVH indices that were reported before the isocentre shifts, the NTCP for the both the lung and the heart were calculated (table 3). These values show a mean value of 1.67% (range 0.73-3.4%). A maximum lung NTCP of 3.4 was reported in a patient with 3cm central lung distance (CLD). The heart NTCP was 0 for all the patients recruited. All the patients had a central lung distance of 3cm or less and an average maximum heart distance (MHD) of 1.4cm.

b. NTCP calculations after set-up error simulations.

Table 7- 9 shows the population mean for the calculated lung and heart NTCP values before and after the 0.3cm, 0.5cm and 1cm isocenter moves (n=12). These values were compared with the baseline values before the shifts. The relative changes were then quantified as a percentage and tested for statistical significance. Consistent with the DVH indices, the maximum calculated population mean NTCP was in the AP direction after a 1cm shift. This was a 144% ($p<0.001$) relative change compared to the value before the shift.

DISCUSSION

Radiation Induced Pneumonitis Complication Probability

The NTCP data reported in this study for the radiation pneumonitis endpoint are in agreement with most published reports of NTCP values ranging from 1-5%. This range is comparable to the NTCP recorded in this study before set-up error simulations. In 67% of the patients (n=8), the mean NTCP values were less or equal to 2%. Hurkman (24) reported lower values between 0% and 1% using the Lyman- Burman- Kutcher (LKB) Model. After performing set-up error simulations with 0.3cm, 0.5cm and 1cm shifts in the x, y and z directions. The maximum percentage variation in NTCP value for the 0.3cm isocenter shift was 78% recorded in the anterior –posterior direction. With 0.5cm shifts, the maximum relative NTCP was 121.6% recorded in the anterior –posterior direction ($p<0.0001$). A maximum value of 144% was recorded with 1cm posterior set-up errors ($p<0.001$). It is important to note that even with the very high percentage differences recorded, the highest absolute maximum ipsilateral lung NTCP value recorded was 5.81%.

Excess Cardiac Mortality Complication Probability

The NTCP for excess cardiac mortality was 0% for all patients. These results are in close agreement with O Kyu Noh *et al* (25) who reported NTCP values for excess cardiac mortality of 0.0% in 2-field treatment plans. O Kyu Noh *et al* (25) also reported an NTCP value of 0.7% for the three-field plans and 1.7% for the reverse hockey stick techniques using the relative seriality model. Gagliadi *et al* cautions that NTCP values >5% could jeopardise the beneficial effect on survival (14).

The cardiac NTCP results in this study are in agreement with studies that used the Lyman Burman-Kutcher model for reporting cardiac complications. It is evident that set-up errors up to 1cm do not have a significant effect on the cardiac NTCP. Higher NTCP values are

reported in studies that used the relative seriality model which is frequently used for assessing cardiac mortality and was used by Gagliadi and colleagues (14), who presented clinical data on excess cardiac complications in breast cancer and recorded mean NTCP values between 1.6 and 2.3%. This deviation from our results may be expected since patients Gagliadi and colleages were treated for the internal mammary nodes with oblique incident electron or photon fields which administered more radiation dose to the heart.

Variation in Pulmonary and Cardiac Dose Volume indices.

Graham *et al* (28) found that the percentage of the ipsilateral lung receiving a dose larger than 20Gy was significantly correlated to the grade of pneumonitis. Similarly, the V25 and the mean cardiac doses have been used as indicators of cardiac complications in breast cancer. In the current research study the DVH indices for both the ipsilateral lung and the heart were calculated.

The Quantec recommend show that the heart V25 should be <10% based on 1% risk of cardiac mortality. In addition, the V20 for the ipisilateral lung should be less than 20%. However, based on table 6, heart tolerance is exceeded after 1cm anterior-posterior (AP), right –left (RL) and left –right (LR) directional moves. The DVH reports also show that 1cm posterior shifts caused the greatest deviation in lung tolerance. In 58% of the patients (n=7), V20 was out of tolerance based on the Quantec reviews (13, 16). This suggests that errors should be strictly kept below 1cm to minimize risk of cardiac complications.

Tissue density corrections and choice of algorithms.

There is need for great caution in comparing the NTCP calculations in treatment planning. Gagliadi (14) cautions that if inhomogeneity corrections for the low density lung tissue are not made in the treatment plans, the heart dose is underestimated, and this affects the use of the NTCP calculations and the volume-based predictions. The lung V20 has been found to be sensitive to the choice of the algorithm used. However, the values for the heart complications have been found to be relatively insensitive to the choice of algorithm. The calculation algorithm used for treatment plan optimization in this study was the superposition algorithm which uses the collapsed cone convolution algorithm and is far more accurate than the routinely used FFT convolution in the presence of tissue in homogeneities (15).The current investigation made sure that lung NTCP parameters and DVH parameters were from 3D conformal studies such as those quoted in the recent Quantec reviews (14, 16).

Clinical Implications

There is need for radiation oncologists to be aware of the implications of the reported NTCPs in left sided breast cancer patients. With improved survival rates in the treatment of breast cancer, long term risks of radiotherapy become relevant.

It is becoming common in most radiotherapy practices to shape the field with a heart block to reduce cardiac exposure. As proposed by Gagliadi *et al* (6), cardiac risk could be substantially reduced by partially blocking the heart using multi-leaf collimators (MLCs) in treatment planning. Raj *et al* (26), recommends that although this is a reasonable method to limit cardiac dose, it should be used cautiously especially in inferiorly located tumour beds. However, it is crucial to know that the reported NTCPs in this study are for standard tangential radiation with 50Gy in 25 fractions. Higher doses and therefore higher risk of

complications may be reported for different treatment regimens. For example, Andratschke *et al* (27) reported doses in hypo-fractionation schemes that are higher than the results in this study after correction of the fractionation efforts using the linear quadratic model (LQ-Model) and a/b ratio.

Limitations

The results of this study are based on the LKB model for calculating NTCPs. It could have been beneficial to use the relative seriality model for assessing the risk of excess cardiac mortality as it has been widely described in literature. CMS XiO V4.16 treatment planning only used the LKB NTCP model. Despite of this limitation, the Quantec reviews reports that although the Lyman-Kutcher-Burman model is not considered the best model, it cannot be rejected as a good fit of the data (11).

CONCLUSIONS

The simulation of set-up errors in all the 3 directions (x, y, and z) shows that the isocentric shifts in the posterior direction have the most significant impact on the DVH data for both the lung and the heart. Pulmonary complications could be minimized if overall set-up errors of more than 5mm are avoided in any single direction. However, the cardiac NTCPs calculated with the standard tangential techniques resulted in zero complication probability for the whole heart.

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Conflicts of Interest

None.

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Figure 1. Schematic view of the NTCP calculation (adopted from Kwa et al (23)

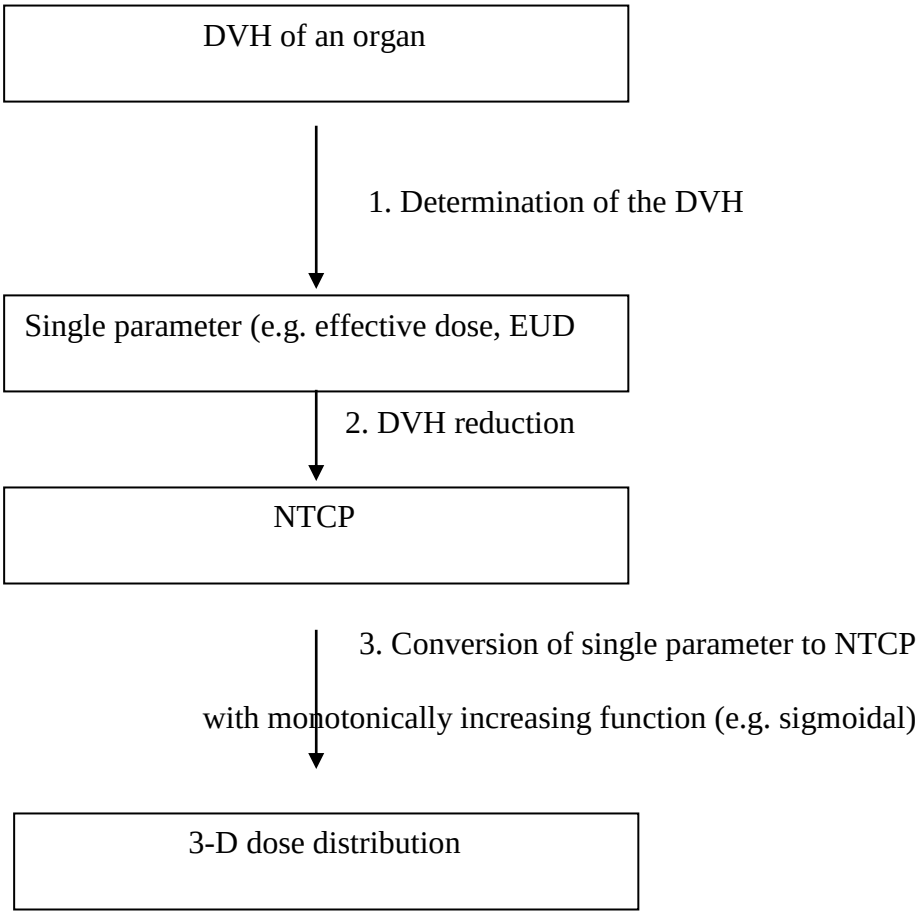

Table 1. Parameters used for NCTP calculations for the Heart and Lung using the LKB model.

Parameter	**OAR**	
	Heart	Lung
D50 (Gy)	48	37.6
m	0.10	0.35
n	0.35	1
a/b (Gy)	3	3
Reference volume	Whole heart	Ipsilateral Lung
End point	*Excess cardiac Mortality*	Pneumonitis *(Any Grade)*
Reference	*Canney et al (33)*	*Semenenko and A Li (84)*

Table 2. Ipsilateral Lung and Heart DVH indices before set-up error simulations (n=12).

Patient No.	Lung (V_{20})	Mean Dose (Gy)	Heart (V_{25})	Mean heart Dose (Gy)
1	10.5	5.43	1.29	2.17
2	14.6	8.57	3.74	3.34
3	12.5	6.38	4.99	3.81
4	12.2	6.49	11	7.21
5	16.8	8.9	4.21	13.89
6	17.6	9.34	4.82	4.02
7	20.45	10	7.28	5.78
8	20.68	10.37	7.3	6.54
9	20.35	11.45	8.14	5.58
10	12.8	6.8	10.2	9.9
11	21.8	11.6	7.28	5.78
12	16.8	8.91	7.3	5.5
Median	*16.8*	*8.9*	*6.1*	*5.7*
Mean	*16.38*	*8.66*	*6.3*	*6.4*
Range	*10.5-21.8*	*5.43-11.6*	*1.29-11*	*2.7-13.89*

Table 3. The calculated ipsilateral Lung and heart NTCPs before set-up error simulations (n=12).

Patient No.	CLD (cm)	Lung NTCP (%)	MHD (cm)	Cardiac NTCP (%)
1	1.6	0.73	0.9	0
2	1.8	0.78	1.0	0
3	2	0.89	1.3	0
4	2	0.91	1.4	0
5	2	1.46	1.5	0
6	2	1.59	1.5	0
7	2.5	1.81	1.5	0
8	2.8	1.93	1.5	0
9	2.9	2.35	1.5	0
10	3	2.35	1.5	0
11	3	2.42	1.6	0
12	3	3.40	1.7	0
Median	2.25	1.59	1.5	0
Mean	2.38	1.67	1.4	0
Range	1.6-3	0.73-3.4	0.9-1.7	0

Table 4. Comparison of volume with 0.3cm isocenter shifts for the heart (V25) and the ipsilateral Lung (V20).

OAR	**No Shift**	**0.3cm Shift**		
	Mean	*Mean*	*Relative change (%)*	*p value*
Ipsilateral Lung *(V20)*				
A-P	16.43	18.9	15.0	0.007
R-L	16.43	17.7	-25.0	0.001
L-R	16.43	17.7	7.70	0.001
S-I	16.43	17.2	4.68	0.001
I-S	16.43	15.9	-3.47	0.006
Heart *(V25)*				
A-P	6.26	8.24	47	0.003
R-L	6.26	9.5	31.5	0.082
L-R	6.26	9.33	51.6	0.003
S-I	6.26	8.96	37.6	0.004
I-S	6.26	8.57	37	0.0017

Table 5. Comparison of volume with 0.5cm isocenter shifts for the heart (V25) and the ipsilateral Lung (V25).

OAR	**No Shift**	**0.5cm Shift**		
	Mean	*Mean*	*Relative change (%)*	*p value*
Ipsilateral Lung				
A-P	16.23	20.93	27.3	0.00015
R-L	16.23	14.09	-14.2	<0.0001
L-R	16.23	19.11	16.31	<0.0001
S-I	16.23	17.78	8.55	0.001
I-S	16.23	15.89	-5.66	0.004
Heart				
A-P	6.26	10.3	60	0.0004
R-L	6.26	8.23	24	0.14
L-R	6.26	9.5	52	<0.0001
S-I	6.26	9.33	49	<0.002
I-S	6.26	8.23	31.6	0.0046

Table 6. Comparison of volume with 1cm isocenter shifts for the heart (V25) and the ipsilateral lung (V20).

OAR	**No Shift**	**1cm Shift**		
	Mean	*Mean*	*Relative change (%)*	*p value*
Ipsilateral Lung				
A-P	16.43	23.3	41.8	<0.0001
R-L	16.43	11.79	-28	<0.001
L-R	16.43	21.25	29.3	<0.0001
S-I	16.43	18.9	15	0.0004
I-S	16.43	14.19	13.6	0.002
Heart				
A-P	6.26	12.57	101.3	0.0002
R-L	6.26	8.04	28.6	0.311
L-R	6.26	10.65	70	<0.0001
S-I	6.26	9.97	59	0.002
I-S	6.26	7.9	26	0.133

Table 7. The populations means for the calculated lung and heart NTCP values before and after the 0.3cm isocenter moves (n=12).

OAR	No Shift	0.3cm Shift		
	Mean	*Mean*	*Relative change (%)*	*p value*
Ipsilateral Lung				
A-P	1.064	1.90	78	0.007
R-L	1.064	1.49	40	0.081
L-R	1.064	2	87.9	0.0005
S-I	1.064	1.72	61.6	0.064
I-S	1.064	1.54	44.7	0.768
Heart				
	0	0	0	0	0

Table 8. The populations means for the calculated lung and heart NTCP values before and after the 0.5cm isocenter moves (n=12).

OAR	No Shift	0.5cm Shift		
	Mean	*Mean*	*Relative change (%)*	*P value*
Ipsilateral Lung				
A-P	1.064	2.36	121.6	<0.0001
R-L	1.064	1.33	25.0	0.081
L-R	1.064	2.15	102.1	0.0001
S-I	1.064	1.84	72.9	0.064
I-S	1.064	1.5	40.9	0.431
Heart				
	0	0	0	0

Table 9. The populations means for the lung and heart NTCP values before and after the 1cm isocenter moves (n=12).

OAR	**No Shift**	**1cm Shift**		
	Mean	*Mean*	*Relative change (%)*	*p value*
Ipsilateral Lung				
A-P	1.064	2.6	144	0.001
R-L	1.064	1.2	127.8	0.0027
L-R	1.064	2.3	116	0.0001
S-I	1.064	1.89	77.6	0.0052
I-S	1.064	1.3	22	0.009
Heart				
	0	0	0	0	0